Review Article

Gynecology & Obstetrics Research

How does Antimullerian Hormone Explain the impairment of folliculogenesis in PCOS, its effects on the dysfunctional gonadotropin control, besides its implication in transgenerational transfer of PCOS-A Systematic Review

Kulvinder Kochar Kaur[1*], Gautam Allahbadia[2] , Mandeep Singh[3]

1. M.D., Scientific Director,
   Dr Kulvinder Kaur Centre for Human Reproduction
   Punjab, India

2. M.D.(Obstt&Gynae),D.N.B, Scientific Director,
   Ex-Rotunda-A Centre for Human Reproduction
   Mumbai, India

3. M.D.DM.(Std)(Neurology), Consultant Neurologist
   Swami Satyan and Hospital, Punjab, India

***Correspondence:**

Dr. Kulvinder Kochar Kaur
Email: kulvinder.dr@gmail.com
Cell: 91-9501358180

Received: 14 MAR 2021 **Published:** 27 MAR 2021

Citation: Kulvinder Kochar Kaur[1*], Gautam Allahbadia[2] , Mandeep Singh[3]
How does Antimullerian Hormone Explain the impairment of folliculogenesis in PCOS, its effects on the dysfunctional gonadotropin control, besides its implication in transgenerational transfer of PCOS-A Systematic Review

Abstract

Earlier we had reviewed on the different classification methods of Polycystic ovary syndrome (PCOS) ,the work of Sir –Petermann and Ibanez group in prepubarchal girls in PCOS and correlation with antimullerian hormone (AMH) amounts and different forms of therapy in PCOS].Here we tried to review the newer aspects of AMH association with PCOS pathophysiology ,its role and interaction with androgens,FSH,LH,their receptors besides influence of invention of AMH receptor2 (AMHR 2) ,the influence of AMH on hypothalamic-pituitary-gonadal(H-P-G) axis influencing Gonadotropin releasing hormone(GnRH) physiology ,gonadotrope function as well as its role in transgenerational transmission of PCOS. Thus here we conducted a systematic review with regards to role of AMH in replacing the USG in PCOS and its pathophysiology in contributing to PCOS. We utilized search engine pubmed,google scholar ;web of science ;embase; Cochrane review library utilizing the MeSH terms like PCOS;AMH; Rotterdam criteria; Insulin resistance ; hypothalamic-pituitary -gonadal(H-P-G) axis influence ;animal studies ;human studies; transgenerational transfer of PCOS ;effects of exaggerated prenatal androgens on offspring; Role of Vitamin D from 1990's to 2021 till date. We found a total of 600 articles out of which we selected 71 articles for this review. No meta-analysis was done. Here we discuss the various points in detail utilizing clinical experiments along with animal studies to validate the posits .Besides the lot of research avenues opened up a lot of exciting development might be in the pipeline, i.e. the generation of AMRH2 antagonists which might aid in the selection of a dominant follicle (DF) without the need for ovarian stimulation and hence financial burden along with risk of ovarian hyper stimulation syndrome (OHSS) gets circumvented.

Key Words;

AMH; PCOS; androgens; FSH; LH; Aromatase; follicular maturation.Gn RH

1.Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrine aberration in women from childbearing age that becomes the commonest aetiology of hyperandrogenism (HA) as well as oligoanovulation (OA) resulting in infertility [1].The properties of PCOS are an escalated amount of ovarian follicles at all growing stages [2, 3].This escalation is Specifically observed in the preantral as well as small antral follicles. Intriguingly, it is exactly these follicles that are basically responsible for generation of antimullerian hormone (AMH)[4].Liberation of AMH from the granulosa cells(GC) of the antral follicles results in serum amounts that we can measure as well as these amounts have demonstrated to be associated with the numbers of generating follicles within the ovaries. The generation of sensitive assays has aided in measurement of the serum AMH as well as its amounts was observed to be2-4 times > in PCOS women in contrast to healthy women. This escalated serum AMH amount was earlier believed to be proportional to the escalated stock of preantral as well as small antral follicles within the PCO [5]. Additionally, it could occur secondary to escalated generation of AMH/follicle [6], in view of the intrinsic characteristics of GC's in PCO.Earlier we had reviewed on the different classification methods of PCOS, the work of Sir –Petermann and Ibanez group in prepubarchal girls in PCOS and correlation with AMH amounts and different forms of therapy in PCOS [7-10]. Thus here we conducted a systematic review with regards to role of AMH in replacing the USG in PCOS and its pathophysiology in contributing to PCOS.

Methods

We utilizing search engine pubmed, google scholar ;web of science ;embase; Cochrane review library utilizing the MeSH terms like PCOS;AMH; Rotterdam criteria; Insulin resistance ; hypothalamic-pituitary-gonadal(H-P-G) axis influence ;animal studies ;human studies; transgenerational transfer of PCOS; effects of exaggerated prenatal androgens on offspring; Role of Vitamin D from 1990's to 2021 till date.

Results

We found a total of 600 articles out of which we selected 71 articles for this review. No meta-analysis was done. This escalation in serum AMH amounts in PCOS fascinated the PCOS specialists who observed it as a method of avoiding the heterogeneity of the Ultrasonography(USG) detailing of PCO morphology (PCOM),utilized to detail as well as define PCOS.Actualy the antral follicle count(AFC) is based on the kind of material utilized .Certain investigators evaluated the diagnostic significance of the serum AMH assay in the form of surrogate to the follicles numbers per ovary(FNPO)[reviewed in 11].Ultimately marking the escalated amounts of antral follicles in women with PCOS.This AMH assay might soon obviate/ as well as or finish the USG ovarian morphology criterias utilized for diagnosing PCOS[12].Apart from its significance for diagnosis ,the observation of an escalated serum AMH amount in PCOS has initiated main pathophysiological problems. Firstly significance has been given to its positive correlation with HA[5[II)Further studies have documented an association with PCOS phenotypes, the way definition has been given by the Rotterdam's criteria((phenotype A; amenorrhea or oligomenorrhea+HA+ Polycystic ovary morphology (PCOM) ;B- amenorrhea or oligomenorrhea+HA; then phenotype C is HA + Polycystic ovary morphology (PCOM) as well as phenotype D amenorrhea or oligomenorrhea+PCOM).Maximum serum AMH amounts are observed to be in phenotype A[13].On the other hand mean AMH amounts were observed to be lesser in hyperandrogenic but eumenorrheic subjects(phenotype C) in contrast to those presenting with amenorrhea or oligomenorrhea[14],despite them not possessing escalated androgens(phenotype D[15].This could imply that the escalated AMH amounts represents a hallmark of a GC dysfunction which has a key part in the anovulation of PCOS,despite other attributors like hyperandrogenism as well as /or escalated LH liberation along with/or hyperinsulinism[16]. Other than the autocrine part of AMH in the impairment of GCs of PCO ,the recent finding of the AMH receptor in a considerable subset of the only study till now could not verify this posit.

GnRH neurons points to probable extragonadal actions of AMH in the hypothalamic-pituitary -gonadal(H-P-G) axis[17],which might get accelerated in PCOS.Ultimately ,recent results point that AMH might be implicated in the epigenetic reprogramming which is now thought to be the major mode that results in PCOS at puberty as well as adulthood[18].

2. How AMH is implicated in the abnormal Folliculogenesis in PCOS

2.1. Is there overexpression of AMH at the Follicular level?

The posit of a part for AMH in the Follicular impairment of PCOS presumes that the expression of this hormone is accelerated within every follicle as well as /or that its signalling pathways are exaggerated. It is tough to illustrate in vivo since the escalation of growing ovarian follicles up to the stage of small antral follicles) in PCOS ladies [2], becomes an additive factor. Actually this by itself could reason out the escalation of AMH amounts since it is these follicles which physiologically liberate AMH [19]. Additionally, an association has further been illustrated with among plasma AMH amounts as well as the extra 2-5mm of antral follicles on USG[5].Hence it has been taken that the escalation in granulosa mass in view of the escalation of growing follicles offers a reasoning that partly the escalated amount of AMH in PCOS ladies[11,20].

Without ruling out the initial one another reasoning offered might be an escalated liberation of AMH that is intrinsic to these developing follicles of PCOS ladies[6,21].Certain publications documented a significant escalation in the AMH/AFC ratio in PCOS ladies in contrast to women displaying asymptomatic USG PCO appearance as well as non PCO controls[4,22].This points to a probable overexpression of AMH by the granulosa cells from antral follicles in PCOS ladies. Akin to this Pellatt etal.[23], documented in vitro in GC cultures obtained from oophorectomy specimens that the AMH amounts in the culture media was 4fold greater in Normoovulatory PCOS ladies as well as 75 fold greater in an ovulatory PCOS ladies in contrast to GCs from control ladies. Further Das etal. [24], in *in vivo* studies emphasized that AMH amounts in follicular fluid of 4-8 mm antral follicles was 5 fold greater, not related to any ovarian hyperstimulation(OHS) setting . Escalated transcription of the AMH gene was illustrated by Catteau-Jonard et al.[25], along with its receptor by quantitative RT-PCR on partly luteinized GCs acquired at the time of oocyte pick up(OPU) for IVF in PCOS women in contrast to control ladies. The escalated transcription was observed in selected intermediate sized (8-13 mm mean dia) as well as larger chosen DF's (17-22mean dia).This whole results point to escalated expression of AMH by the GCs from women with PCOS, possibly due to intrinsic impairment of these cells .

However this posit is not agreed on by all groups. No variation in transcription of AMH gene or its receptor was observed by Owens etal.[26],in the study they conducted where contrasting of the expression of 13 genes by quantitative PCR by GC's from small, unstimulated antral follicles(on ovarian cortex that had been sampled for fertility preservation) along with on partly luteinized GC's(in patients undergoing in vitro fertilization[IVF])from PCOS ladies in contrast to GCs from control ladies. Conversely Dilaver et al.[27], observed no basal escalation in AMH expression in transcripts in cultured human GC's from PCO in contrast to normal ovaries. Such findings however should be analyzed, considering the low amounts of AMH expression in cultured human GC's in vitro the small cohort of cases that were evaluated.

At the Molecular level another method of reasoning might be an escalated stability of the messenger RNA secondary to the transcription of AMH gene in the GC's from PCO women. Hence despite transcription of AMH gene is not escalated, an accelerated stability of the messenger RNA could result in greater marked translational activity as well as hence to an enhancement of AMH liberation. The extent of polyadenylation of the3' untranslated region (3'UTR) of mRNA's coding for AMH could be one of the reasoning. Nevertheless, the part of some Micro RNA's that are understood to be inhibitors of the translation of Messenger RNA also might be quoted.

2.2. If True the Reason Behind escalated generation of AMH by GC's From PCOS Ovaries?

Molecularly, no aberrations in the AMH genes which might result in escalated transcription have got demonstrated. A full study series suggest how hyperandrogenism is responsible ,but altercation continues in view of the actual existence of this action that might be direct or indirect .Controversial in vivo results in PCOS exist .A probable direct stimulatory action of androgen on the expression of AMH by GC's was initially brought up on getting a positive association with AMH along with androgen amounts got documented in a lot of series of PCOS ladies[5,29,30]. Nevertheless, multiple confounding factors might participate , Specifically the positive action of androgen on the amount of growing ovarian follicles [31] as well as hence on granulose mass.The delivery of androgens in the form of role of female-male transitions stimulated a significant reduction in AMH amounts but this protocol had GnRH agonists ,that might have led to confusing outcomes by reducing serum FSH amounts .The reduction in serum AMH amounts in PCOS ladies getting high amounts of cyproterone acetate, that is a progestin possessing robust ant gonadotropic as well as peripheral anti androgenic effect was not higher than when under other ant gonadotropic drugs ,like estrogen –progesterone amounts [33,34]. Nevertheless, again serum FSH amounts are less in these settings.

Akin to that in vitro experimental results are controversial. An androgen inhibiting action of androgens on the liberation of AMH by sertoli cells in men has been properly illustrated for last lot of yrs. [35].That high dose T was the one resulting in reduction in AMH amounts from the GC's of small bovine follicles was illustrated by Criosto etal. [36].Contradicting this Zhang etal. [37], documented that testosterone (T) led to an escalation in AMH mRNA's amounts in GC's from mouse antral follicles. No action in women has been illustrated by certain researchers of 5α dihydrotestosterone (DHT) on the expression of AMH in GC's from control women, while an escalation was observed only in GC's from PCOS ladies [38, reviewed in 39]. Dilaver et al.[27], further found this dose based actions of DHT, where that of T was either positive or nil as per its amounts in the GC culture medium. Noticeably the conflicting outcomes among these studies regards to the actions of androgens on expression of AMH might have been reasoned out by the large differences in the models utilized (various animal species, cell types ,methods of evaluation).Furthermore the actions of androgens has to be looked at in the complicated Crosstalk they do with other significant players at the GC's level ,like FSH as well as estradiol(E2),that differs as per the follicular stage as well as those that are not considered in the experimental studies (figure1)[20].

Various studies point towards an indirect actions of androgens, through an escalation of the amount of FSH receptors (FSH R) as well as /or estradiol receptors(ER-α).a lot of studies converge towards the facilitating effects of androgens on the transcription as well as translation of FSH R via genomic as well as non-genomic actions along with this actions is probably escalated in PCO (review in ref 20]. Ssubsequently ,the stimulation of recombinant follicle stimulating hormone (FSH) on AMH expression which takes place in small growing follicles from normal ovaries would get amplified in PCO[40].This might take place till no aromatase expression, since E2 inhibits AMH expression via the receptors(ER-β)[41](figure1).

This action might be dysfunctional in GC's from PCO. Dilaver et al.[27], documented that abundant androgens escalated the ratio of ER-α/ ER-β causing an escalated AMH expression. The significance of relative expression amounts of ER-α as well as ER-β has been demonstrated earlier[42].Recently a significant positive association among the ratio of ER-α/ ER-βtranscripts as well as the amounts of AMH as well as an escalation of ER-α in cultured transcripts in cultured GC's from PCOS women. Nevertheless,, small growing follicles generate minute amounts of E2 as well as this action of androgens via ER-α activation may not be applicable in vivo. On the other hand during the time of selection of antral follicles for dominance as wel as when activation of ER-β is the determining factor ,this action of androgens sustained AMH expression may be part of the mode resulting in follicular arrest of PCOS.

2.3AMH Signalling Pathways in PCO-GC's

Besides the escalated AMH expression, the expression of type2 AMH receptors(AMHR2)is exaggerated in PCO-GC's[25,38].With the activation of AMHR2,a marked escalation in phosphorylation of SMAD 1,5,8 in the mouse[43], as well as of SMAD5 in luteinized human [44] .Interestingly Dilaver et al.[27], illustrated recently in cultured GC's from PCOS women, a dose based reduction in phosphorylation of SMAD 1,5,8(P- SMAD 1,5,8)once AMH is existing, whereas surprisingly the amounts of transcripts of P-SMAD1,5,8 was escalated by roughly50% in controls (although not reached statistical significance).It is apparent that if the involvement of AMH Signalling Pathways in PCO are impaired ,it becomes asignificant issue ,although other further studies are required, particularly regarding the implication of SMAD's that are inhibitory.

2.4The impact of Escalated AMH on ovarian follicles, As per Stages

i) Early follicular Development Is Slowed Following Escalated AMH

This posit is dependent on the original work of Durlinger etal.[45].Once AMH was added to the cell culture media that possessed follicles from knockout mice for the AMH gene, displayed follicular development, even once FSH was existing ,pointing to an inhibitory action of AMH on FSH based proliferation of GC's.

Once there is a condition where high AMH exists like PCOS,a reduction of the initial FSH-sensitive follicular development could hence take place as well as result in the collection of the amounts of developing follicles within the ovaries of these patients. Nevertheless, little data particular to human species have validated this patho physiological posit [3].

ii) Escalated AMH reduces Apoptosis of GC's in Small follicles

Certain workers have pointed that AMH possesses an antiatretic action on developing follicles at the time of early follicular recruitment [27, 46]. Certain agents possessing proapoptotic activity like Vitamin D as well as leptin might work by reducing the AMHR2 expression as well as hence the anti-apoptotic activity of AMH on GC's[476.

Little amount of data are present in the literature for PCOS ladies with regards to this, In the cell culture models a lesser Apoptosis rate of GC's from preantral follicles was illustrated by Weber et al.[47], in contrast to controls .By immunochemistry GC's from PCO are lower as well as get stained more often for the markers of Apoptosis as well as anti-Apoptosis in contrast to controls respectively [24,48].High AMH amount might be directly implicated in this event ,that would end in accumulation for later utilization action [49],that aids in the escalation in the amount of developing follicles in the PCOS.

Lastly, once reaching menopause reaches PCOS ladies have significantly greater serum AMH amounts in contrast to non-PCOS ladies [50].

iii) Escalated AMH results in follicular arrest in large antral follicles

This action occurs secondary to complicated Crosstalk among AMH, aromatase, ER's as well as probably LH (figure1)

AMH has been demonstrated to significantly reduce besides FSHR expression, ovarian aromatase [rev in 19]. Physiologically, this confers protection to small follicles from premature aromatase getting expressed. Once this protective action becomes more than ,in view of its demands of its Physiological part, escalation as well as /or since it persists for longer duration than needed ,it could result in a defect in the selection of the dominant follicles (DF),resulting in what is labelled as ''follicular arrest ''.The explanation that AMH inhibits the FSH-based factors essential for dominance of follicles, gives a lot of significance to the escalated amount of AMH in PCOS, thus making AMH a central actor in 'follicular arrest. In accordance with that it has been illustrated that before the DF emerges in case of anovulatory women with PCOS with the utilization of recombinant FSH has an antecedent significant decrease in serum amount of AMH [51].

Additionally, various researchers have illustrated premature expression of Luteinizing hormone receptor (LHR) in GC's from PCOS ladies. This has been pointed to be the main reason for the stoppage of follicular development, observed in PCOS ladies with anovulation [52]. Nevertheless, this posit doesn't appear to be feasible since many other researchers have recently illustrated a negative association among the AMH amounts in the follicular fluid as well as the expression of LHR in GC's[53].

Iv Escalated AMH in follicles Differs as per the PCOS phenotype

AMH overexpression/follicle might vary based on the PCOS phenotype. Hence as per certain researchers ,in a PCOS women's population, the AMH/AFC ratio was significantly greater in anovulation patients in contrast to the ones possessing an ovulatory phenotype(phenotype C or asymptomatic USG PCO)[22,54].On the other hand ,other researchers have illustrated greater AMH amounts in hyperandrogenic PCOS ladies irrespective of the ovulatory status[13,29].This query as regards to the differences in AMH expression as per the PCOS phenotype is quite complicated since the principal component evaluation has demonstrated that the markers of HA as well as OA have a close association[30]. Nevertheless, once both HA as well as anovulation get statistically contrasted with escalated AMH, the correlation is significant with anovulation, while the HA would just be an additive factor to that of the latter [23].

Hence escalated AMH in GC's from PCOS would take place secondary to HA indirectly as well as would be implicated in the exaggerated follicles of PCO along withfollicular arrest in anovulatory patients.

3. How AMH Disrupts Gonadotropin Regulation in PCOS

High LH amount is observed in 50%of PCOS ladies, with a greater prevalence in women without any metabolic dysfunction [55]. This occurs due to the exacerbation of frequency of GnRH liberation, which certain researchers think is secondary to the negative feedback failing in view of prenatal hypothalamus getting exposed to Androgens [56].On the other hand, mean FSH amounts are lesser in contrast to controls in case of a lot of publications with no conclusive reasoning till now. Both processes result in an escalation in the LH/ FSH ratio that was utilized as a diagnostic measure earlier, but got given up as it was very insensitive. MH might be implicated in the Disruption of Gonadotropin function Regulation.

3.1. Existence of a Positive association Among AMH and LH

Serum amounts of AMH and LH possess a Positive association in PCOS ladies [57].This association has been demonstrated to be independent of Serum androgens along with FSH amounts [51].

Whether any causal association exists in this correlation has continued to be a subject of debate. Certain authors say, the etiology would be the great amounts of LH which might activate AMH liberation as well as expression as demonstrated by certain researchers in vitro from luteinized granulosa cells [23, 58]. Nevertheless, in vivo GC's expression of LHR is late ,while AMH generation starts in primary follicles as well as peaks prior to LHR expression [4].In another way, recent experimental results point that AMH possesses greater probability of extragonadal actions as well as Specifically possesses the capacity of escalation of GnRH neuronal activity.Cimino et al.[17], demonstrated that almost 50% of GnRH neurons (both murine along with from adult human) possessed particular receptors for AMH type2(AMHR2).Various in vitro as well as in vivo experiments in combination illustrated that AMH escalated the pulsatile liberation of GnRH based LH via a central effect .Actually electro physiological experiments have documented that exogenous AMH escalated the GnRH neuronal activity of the GnRHneuron, Nevertheless, this might be an indirect effect ,since AMHR2 has a wide distribution in the hypothalamus, thus a synergism in action of other cell kinds ,aiding in escalation of GnRH liberation can't be ruled out[rev in 59].Akin to that Barbotine etal.[59], illustrated that in vivo delivery of AMH (intracerebroventricular) was followed by a dose-based escalation in LH liberation as well as pulsatility .Finally ,the escalation in AMH amounts would result in a chain reaction; i.e. greater liberation via

hypothalamic neurons for GnRH liberation, which would thus escalate the liberation as well as pulsatility of LH by the anterior pituitary gland.

AMH also possesses the capability of acting at the pituitary level as well as regulate the gonadotropic cell activity. Recently it got documented that the expression of mouse as well as human AMHR2 gene in Gonadotropic cell is controlled by GnRH[60].Actually utilization of LβT2 cells ,Hall etal.[61], demonstrated that GnRH liberated at a high frequency (1pulse/30') escalated AMHR2 expression by the Gonadotropic cell, whereas if at lesser frequency (1pulse/2 hr) did not have any action. Nevertheless, the involvement of control of AMHR2 from the pituitary working as a function of GnRH pulsatility has to be demonstrated in humans, particular in PCOS.

These outcomes evoke the posit that the extragonadal effect of AMH could be at the initiation of ,or aid to the vicious cycle of neuroendocrine as well as gonadal control impairment that are seen in PCOS.

3.2. Existence of a Negative association Among AMH and FSH-A Complicated issue

For long it has been demonstrated that low to normal FSH exists in PCOS[61],even ssubsequent to adjusting the body mass index(BMI) as well as the no of2-9 follicles[13].Various studies have documented a Negative association among AMH and FSH amounts [5,51], Nevertheless, no crisp reasoning has been given thus far.It is not possible that this points to a Negative action of FSH on AMH generation. Actually the converse is pointed by conditions of gonadotropic deficiency in which AMH amounts are reduced as well as escalates under endogenous FSH[62].These controversial results demonstrate the complicated association Among AMH and FSH which might work at the ovarian as well as /or hypothalamic-pituitary levels as well as that might differ as per the disease state .In case of PCOS,Dewally etal.[39], posited that by escalating the frequency of GnRH,an escalated AMH amount would escalate the pituitary liberation of LH at the cost of FSH[63]. Greater emphasis has to be put on this problem. Hence newer experimental outcomes point that AMH is implicated in the neuroendocrine disruption in PCOS, Nevertheless, no human literature is present till date for verification of this posit.

4. Implication of escalation in AMH in the Transgenerational Transmission of PCOS

In 2000's the posit of prenatal programming of PCOS in association with gestational HA was first pointed [64]. Subsequent to this invention ,various studies validated in different animal models that high T amounts at the time of pregnancy could result in the PCOS phenotype manifesting in mouse ,ewe as well as nonhuman primate models[rev in 56,65].The posit of androgen associated prenatal programming in PCOS Ladies is corroborated by a full series of studies[18],but the initiation of this gestational HA is still not clear till now.

Recent studies point that AMH might be implicated in this event. Circulating AMH amounts are greater in pregnant women with PCOS in contrast to those with normal fertility[66] as well as are associated with androgen amounts [67].These outcomes hence point that AMH at relatively high amounts during pregnancy by itself be instrumental in programming of PCOS. Experimental, verification was done regards to this[66].Tata etal.[66],showed that the injection of bioactive type of AMH(AMHc)into mice in late pregnancy ,resulted in the manifestation of HA PCOS phenotype in the offspring in adulthood .This model known as PAMH,high AMH amounts during pregnancy caused greater pulsatility of GnRH as well as LH,that resulted in gestational HA. Escalated maternal LH alone or with AMH would further result in reduction in placental aromatase, escalating maternal bioavailable T as well as resulting in fetal exposure of androgen abundance. This would stimulate a cascade within the offspring resulting in escalation in hypothalamic neuronal excitability .In adult offspring, mice demonstrate an escalated excitatory afferents causing an escalation in the excitability of GnRH neuron. In adult offspring, mice display an escalated excitatory afferents that result in an escalation in the excitability of GnRH neuron. This GnRH hyperactivity then activates ovarian steroidogenesis as well as taking part in the vicious cycle

Seen in PCOS by decreasing the Negative feedback of E2 as well as progesterone (P) on LH.Prenatal therapy with a GnRH antagonist in PAMH mice avoids the occurring of the conditions earlier revealed in offsprings [66]. Tata etal. [66], thus illustrated that there is major part of GnRH through AMH in the *in utero programming* event that causes the neuroendocrine aberrations typical of PCOS occurring in the offspring.

Lastly it has to be realized that the new PAMH mouse model points that maternal HA seen in PCOS is due to central effect of AMH on GnRH as well as LH aiding in an escalation of ovarian steroidogenesis as well as an inhibition of placental aromatase expression, resulting in escalation of Bioavailability[66].Agreeing with that continuous delivery of P450 aromatase Inhibitor stimulated PCOS with a metabolic and endocrine phenotype in female rats at adult age[67].Inhibition of placental aromatase expression might be the main mode in the *in utero* programming of PCOS since serum maternal androgens as well as LH amounts are not that much escalated as in PAMH mice .A reduction in placental aromatase has efficaciously been seen in PCOS ladies who have had child birth[68].Thus mice studies offer significant newer ways that need to be verified in women ,as the mouse model is periovulatory as well as can't get superimposed in human situation with perfection.

Thus maternal escalated AMH might be one of the etiologies for *in utero programming* of PCOS, for certain subset of PCOS patients at least.

5.Conclusions

Further in a study conducted by Sahmay et al. [69] the prevalence of IR was 45%. The prevalence of IR was 57% in women with BMI ≥ 25. Serum AMH levels were not significantly different among women with and without IR.(n=293total) Also, HOMA-IR values were not significant among different AMH percentiles. However, in each AMH percentile BMI were found to be higher in women with IR than in women without IR. The median HOMA-IR values were the highest in women with BMI ≥ 25 in both IR (+) and IR (-) groups. No significant difference was found among PCOS phenotypes in terms of HOMA-IR and BMI. Positive correlations were found between BMI, free testosterone and HOMA-IR. However, No correlation was found between AMH and HOMA-IR.Thus concluding that the serum AMH levels among women with IR and without IR in PCOS were not significantly different. Also, we did not observe a correlation among serum AMH levels and IR in women with PCOS. IR was not correlated with different PCOS phenotypes either. We found a positive correlation between BMI and IR. IR should be investigated in women with PCOS having a BMI ≥ 25, independent of their phenotype or AMH levels.

On the contrary in another study conducted by

Wiweko etal. [70], in a cross-sectional study implicating reproductive age women aged 18-35 years. Subjects were recruited consecutively at an Indonesian Hospital among 2011 until 2014. PCOS women diagnosed using 2003 Rotterdam criteria were categorized into four different PCOS phenotypes. Subsequently, serum level of AMH and HOMA-IR was measured and evaluated with association tests done using SPSS 11.0 RESULTS: A total of 125 PCOS patients were included in a study conducted within a 3-year period. Phenotype 1 (anovulation, HA, and polycystic ovaries) demonstrated the greatest amounts of AMH and HOMA-IR, which decreases in accordance to severity level ($p < 0.005$). The positive association between AMH and HOMA-IR persisted even after adjusting for BMI in multivariate analysis. There was a positive correlation between serum AMH and HOMA IR levels. Serum AMH and HOMA IR levels were significantly different across the four PCOS phenotypes; with the highest values were present with phenotype 1[70].

In another cross-sectional study utilizing a retrospective chart review of 128 patients aged 12-20 referred to an academic adolescent gynecology and endocrinology clinic for an evaluation of suspected PCOS. Unadjusted comparisons of AMH and 25(OH) D distributions among subjects with and without PCOS were performed using the

Wilcoxon Rank Sum test. Quantile regression was used to compare the median AMH and 25(OH) D among subject groups; adjusting for race, ethnicity, BMI, insurance type, age, and season when blood work was done. Seventy-four subjects were classified as having PCOS by meeting ≥2 of the three Rotterdam diagnostic criteria, and 47 subjects met only one Rotterdam diagnostic criteria, and were utilized as the comparative non-PCOS group. There were statistically significant unadjusted variations in median levels of AMH and 25(OH)D. In the adjusted analyses, median AMH was significantly greater in the PCOS group compared to the non-PCOS group (+ 2.39 ng/mL, 95% CI 0.43, 4.35, $p = 0.018$);

25(OH)D was significantly lower in the PCOS group (-9.01 ng/mL, 95% CI -14.49, - 3.53 p = 0.001). In our sample, adolescents in both groups had insufficient 25(OH)D level (22 ng/mL) and elevated BMI (32.2 kg/m2).Thus concluding that Adolescents with PCOS demonstrated high levels of AMH and low 25(OH)D levels. Since traditional clinical markers of PCOS may be physiologic in adolescents, AMH and 25(OH) D might get utilized as surrogate markers of PCOS risk in adolescents [71].

Still a lot of information has to be obtained to get insight on the patho physiological part that AMH plays in PCOS.It is clear that the autocrine effect of escalated AMH within the GC's is possibly the major factor in the implication in folliculogenesis as well as an ovulatory condition. Nevertheless, the recent invention of its endocrine action of retro regulation on the hypothalamus as well as the placenta has opened a lot of avenues for future research that has the chances of resulting in newer curative or even avoiding therapies. Like when we can acquire them antagonists of the AMHR2 may aid in reducing the LH as well as follicle escalation as well as hence to enhance the chances of a DF emerging along with escalating the possibility of a pregnancy without requiring any kind of ovarian stimulation.

REFERENCES

1. Norman RL, Dewailly D, Legro RS, Hickey TE.Polycystic ovary syndrome. Lancet 2007; 370:685-97.
2. Hugesdon PE.Morphology and Morphogenesis of the Stein Leventhal ovary and of so called ''hyperthecosis''Obstet Gynaecol Surv 1982; 37:59-77.
3. Webber LJ,Stubbs S,Stark J,Trew JH,Margara R,Hardy K,etal.Formation and early Development of follicles in the Polycystic ovary. Lancet 2003;362:1017-21.
4. Bhide P,Dilgil M,Gudi A,Shah A,Akwaa C,Homburg R,etal.Each small antral follicle in ovaries of Women with Polycystic ovary syndrome produce more antimullerian hormone than its counterpart in a normal ovary: an observational cross-sectional study .Fertil Steril 2015; 103:537-41.
5. Pigny P,Merlen E,Robert Y,Cortet-Rudelli C,Decanter C, Jonard S, etal. Elevated serum level of
6. Antimullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicles excess and to the follicular arrest .J Clin Endocrinol Metab 2003; 88:5957-62.
7. Pellat L, Rice S, Mason HD. Antimullerian hormone and Polycystic ovary syndrome: a mountain too high? Reproduction 2010; 139:825-33.
8. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Controversy Regarding Classification of Polycystic Ovary Syndrome (PCOS) Remains Unresolved with Newer Classifications Emerging Day by Day in the Complex Syndrome-A Short Communication". *EC Gynaecology* 8.9 (2019): 855-858.
9. Kulvinder Kochar Kaur, Allahbadia GN, Singh M. Utilization of Letrozole and Clomiphene Citrate for Better Optimization of Ovulation Induction Rates in PCOS Patients. Gynecologist. 2019; 1(2): 1008.
10. Kulvinder Kochar Kaur,Allahbadia GN,Singh M.Role of Antimullerian Hormone as an Early Predictor of PCOS in Perimenarchal Girls-Role in Preventing Associated Comorbidities.J Gynaecol 2019;4(1):1-3. **DOI:** 10.23880/oajg-16000175
11. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. "Importance of Ovarian Volume in Determining the Ovarian Reserve as Well as Hormonal Function Besides Determining the Polycystic Ovary Morphology (PCOM) and Classification of Polycystic Ovary Syndrome (PCOS). A Short Communication". EC Gynaecology 9.8 2020;9(8): 25-27.
12.Dewailly D,Andersen CY,Balen A,Broekmans E,Dilaver N,Fanchin R ,etal. The physiology and clinical utility of antimullerian hormone in women. Human Reprod Update 2014; 20:370-85.
13.Fraissinet A, Robin G, Pigny P, Lefebvre T, Catteau-JonardS, Dewailly D.Use of serum antimullerian hormone assay as a surrogate for polycystic ovary morphology: impact on diagnosis and phenotypic classification of Polycystic ovary syndrome. Human Reprod 2017; 32:1716-22.
14. Piouka A,Farmakiotis D,Katsikis I,Macut D,Gerou S,Panidis D. Antimullerian hormone levels reflect severity of PCOS but are negatively influenced by obesity relationship with increased luteinizing hormone levels. Am J Physiol Endocrinol Metab 2009; 296:E238-43.

15. Catteau-JonardS,Bancquart J,Poncelet E, Lefebvre-Maunoury C,RobinG, Dewailly D. Polycystic ovaries at ultrasound :normal variants or silent Polycystic ovary syndrome? Ultrasound Obstet Gynaecol 2012;40:223-9.
16. Sahmay S,Atakul N,Oncul M,Tuten A,Aydogan B,Seyisoglu H.Serum antimullerian hormone levels in the main phenotypes of Polycystic ovary syndrome.Eur J Obstet Gynaecol Reprod Biol 2013;170:157-61.
17. Franks S, Stark T, Hardy K.Follicle dynamics and anovulation in polycystic ovary syndrome. Human Reprod Update 2008; 14:367-78.
18. Cimino I,Casoni F,Liu X,Messina A,Parkash J,Jamin SP,etal.Novel role for antimullerian hormone in the regulation of GnRH neuronexcitability and hormone secretion. Nat Commun 2016; 7:10055.
19. Dumesic D,Hoyos LR,Chazenbalk GD,Naik R,Padmanabhan V,AbbottD.Mechanisms of intergenerational transmission of Polycystic ovary syndrome. Reproduction 2019; 159:R1-13.
20. BroekmansFJ, Visser JA,Laven JS,Broer SL,Themmen AP,Fauser BC. Antimullerian hormone and ovarian dysfunction.TEM 2008; 19:E340-7.
21. Dewailly D,Robin G,Peigne M, Decanter C, Pigny P, Catteau-Jonard S.Interactions between androgens,FSH, antimullerian hormone and estradiol during folliculogenesis in the human normal and Polycystic ovary. Human Reprod Update 2016; 22:709-24
22. Bhide P, Homburg R. Antimullerian hormone and Polycystic ovary syndrome.Best Pract Res Clin Obstet Gynaecol 2016;37:38-45.
23. Alebic MS,Stojanovic N,Duhamel A, Dewailly D. The phenotypic diversity in per follicle Antimullerian hormone production in Polycystic ovary syndrome. Human Reprod 2015; 30:1927-33.
24. Pellat L,Hanna L,Brincat M,Galea R,Brain H,Whitehead S,etal. Granulosa cell production of Antimullerian hormone is increased in Polycystic ovary syndrome. J Clin Endocrinol Metab 2007; 92:240-5.
25. Das M, Gillot DJ, Saridogan E, DjahanbackhchO. Antimullerian hormone is increased in follicular fluid from unstimulated ovaries in Women with Polycystic ovary syndrome. Human Reprod 2008; 23:2122-6.
26. Catteau-JonardS,Jamin SP,Leclerc A,Gonzalez J, Dewailly D,Di Clemente N. Antimullerian hormone, its receptor , FSH- receptor,and androgen receptorgenes are overexpressed by Granulosa cells from stimulated follicles in women with Polycystic ovary syndrome. J Clin Endocrinol Metab 2008; 93:4456-61.
27. Owens LA, Kristensen SG, Lerner A, Christopoulous Glover S, Hanyaloglu AC, etal. Gene expression in granulosa cells from small antral follicles from women with or without polycystic ovaries. J Clin Endocrinol Metab 2019;34:2467-79.
28. Dilaver N, Pellat L, Jameson E,Ogunjimi M,Bano G, Homburg R,etal.The regulation of signaling of Antimullerian hormone in human granulosa cells :relevance to Polycystic ovary syndrome. Human Reprod 2019; 34:2467-79.
29. Sproul K,Jones MR,Mathur R,Azziz R,Goodarzi MO. Association study of four key folliculogenesis genes in Polycystic ovary syndrome.BJOG 2010;117:756-60.
30. Pigny P, Jonard S, Robert Y, Dewailly, D.Serum Antimullerian hormone as a surrogate for antral follicle Count for definition for definition of polycystic ovary syndrome. J Clin Endocrinol Metab 2006; 91:941-5.
31. Dewailly D, Pigny P,Soudan B, Catteau-JonardS, Decanter C,PonceletE,etal.Reconcilng the definitions of Polycystic ovary syndrome: the ovarian follicle number and serum Antimullerian hormone concentrations aggregate with the markers of hyperandrogenism. J Clin Endocrinol Metab 2010; 95:4399-405.
32. Jonard S, Dewailly D.The follicular excess in Polycystic ovaries ,due to intraovarian hyperandrogenism may be the main culprit for the follicular arrest Human Reprod Update
2004; 10:107-17
33. Cansen MR, Soleman RS, Kuijper EA, Kreukels P, DeRooC, Tilleman K, etal. Antimullerian hormone levels decrease in females to male transsexuals using testosterone As cross sex therapy. Fertil Steril 2015;103: 1340-5.
34. Kallio S,Puurunen J,Ruokonen A,Vaskivun T,Piltonen T.TapanianenIS. Antimullerian hormone levels decrese in women using combined contraception independently of contraception route. Fertil Steril 2013;99: 1305-10.
35.Plouvier P, Peigne M,Gronier H, Robin G, Catteau-JonardS,Dewailly D.Is the suppression effect of cyproterone acetate on Serum Antimullerian hormone levels in women

with Polycystic ovary syndrome stronger than under oral contraceptive pill?, Gynaecol Endocrinol 2016;18:1-5.
36. Rey R, Lucas –Croissier C, Lasala C, Redecarras P.AMH/MIS: what we know already about the gene band its regulation.Mol Cell Endocrinol 2003; 211:21-31.
37. Criosto N,Sir –Petermann T,Greiner M,Maliqueo M,Aedo M,etal. Testosterone-induced downregulation of Antimullerian hormone expression in granulosa cells from small bovine follicles. Endocrine 2009; 36:339-45.
38. Zhang Y ,Wang SF,Zheng JD,Zhao CB, Zhang YN,Liu LI,etal.Effects of Testosterone on the expression levels of AMH,VEGF and HIF-α in mouse granulosa cells.Exp Ther Med 2016;12:883-8.
39. Pierre A,Taieb J,Giton F,Grynberg M,Touleimat S,El Hachem H,etal. Dysregulation of the Antimullerian hormone system by steroids levels in women with Polycystic ovary syndrome. J Clin Endocrinol Metab 2017;102:3970-8.

40. Dewailly D, Barbotin AL, Dumont A, Catteau-JonardS, Robin G.role of Antimullerian hormone in the pathogenesis of Polycystic ovary syndrome .Front Endocrinol 2020; 11:641.
41. Pierre A, Peigne M, Grynberg M,Arouche N, Taieb J,Hesters L,etal.Loss of LH-induced down regulation of Antimullerian hormone receptor expression may contribute to anovulation in women with Polycystic ovary syndrome. Human Reprod 2013; 28:762-9.
42. Dumont A, Robin G, Catteau-JonardS, Dewailly D.Role of Antimullerian hormone in pathophysiology, diagnosis and treatment of Polycystic ovary syndrome. A review. Reprod Biol Endocrinol 2015;13:137.
43. Jaikimiuk AJ, Weistman SR, Yen HW, Bogusiewicz ,M,Magoffin DA. Estrogen receptor alpha And beta expression in theca and granulosa cells from women with polycystic ovary syndrome. J Clin Endocrinol Metab 2002; 87:5532-8.

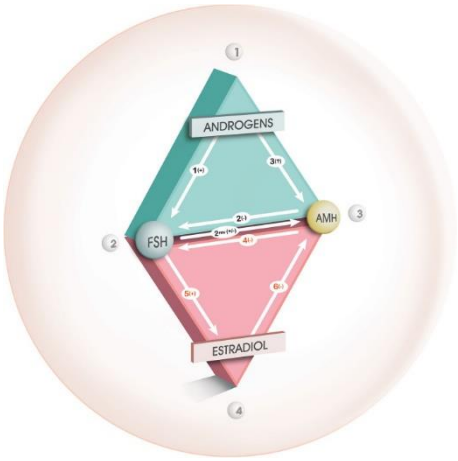
44. Sedes L,Leclerc A,Moindjie H,Cate RL,Picard JY, Di Clemente N,etal. Antimullerian hormone recruits BMPR-1A in immature granulosa cells .PLoSONE 2013; 8:e81551.
45. Prapa E,Vasilaki A,DafopoulousK,Katsiani E,GeorgialiasP,Messini CI,etal. Effects of Antimullerian hormone (AMH)and bone morphogenetic protein(BMP-15)on steroidogenesis in primary cultured human luteinizing granulosa cells through Smad 5 signalling.J Assist Reprod Genet2015;32:1079-88.
46. Durlinger AL,Gruijters MJ,Kramer B,Karels B,Kumar TR,Matzuk MM,etal. Antimullerian hormone attenuates the effects of FSH on follicular Development in the mouse ovary. Endocrinology 2001;142:4891-9.
47. Seifer DB, Merhi Z, Is AMH a regulator of follicular atresia? J Assist Reprod Genet2014; 31:1403-7.

48. Webber LJ,Stubbs S,Stark J, Margara R,Trew JH,Lavery SA,etal.Prolonged survival in culture of preantral follicles from Polycystic ovaries. J Clin Endocrinol Metab 2007; 92:1975-8.
49. Das M, DjahanbackhchO ,Hacihanefioglu B, Saridogan E,Ikram M,Ghali L,etal. Granulosa cell survival and proliferation are altered in Polycystic ovary syndrome. J Clin Endocrinol Metab 2008;93:881-7.
50. Maciel GA,Baracat EC,Benda JA,Markham SA,Hensinger K,Chang RJ,etal.Stockpiling of transitional and classic primary follicles in the ovaries of women with Polycystic ovary syndrome. J Clin Endocrinol Metab 2004; 89:5321-7.
51. Piltonen T,Morin-Papunen L,Koivunen R,Perheentupa A, Ruokonen A, TapanianenIS. Serum Antimullerian hormone levels remain high until late reproductive age and decrease during metformin therapy in women with polycystic ovary syndrome. Human Reprod 2005; 20:1820-6.
52. Catteau-Jonard S , Pigny P, ReyssAC, Decanter C, PonceletE,Dewailly D.Changes in Serum Antimullerian hormone level during low dose recombinant follicle stimulating hormone therapy for anovulation in Polycystic ovary syndrome.J Clin Endocrinol Metab 2007; 92:4138-43.

53. Jaikimiuk AJ, Weistman SR, Navab A, Magoffin DA.Luteinizing hormone receptor, steroidogenesis enzymes messenger ribonucleic acids are overexpressed in thecal andgranulosa cells from polycystic ovaries. J Clin Endocrinol Metab 2001; 86:1318-23.

54. Jeppersen JV,Kristensen SG,Nielsen ME,Humaidan P,Dal Canto M,Fadini R,etal.LH receptorgene expression in human
Granulosa and cumulus cells from antral and preovulatoryfollicles. . J Clin Endocrinol Metab 2012; 97:E41524-31.
55. Bhide P,Kulkarni A,Dilgil M,Dhir P, Shah A, Gudi A,etal.Phenotype variation in Antimullerian hormone (AMH)production per follicle in women with Polycystic ovary syndrome(PCOS) and isolated Polycystic ovary morphology (PCOM):an observational crosssectional study. Gynaecol Endocrinol 2017; 33:801-6.
56. Huang CC,Tien YJ,Chen MJ, Chen CJ,HoHN,Yang YS.Symtom patterns and Phenotypic subgrouping of women with Polycystic ovary syndrome: association between Endocrine characteristics and metabolic aberrations. Human Reprod 2015; 30:937-46.
57. Walters KA,Gilchrist RB,Ledger WL,Teede HJ,Handelsman DJ,Campbell RE.New perspectives on the pathogenesis of PCOS:neuroendocrine origins.Trends Endocrinol Metab 2018;29:841-52.
58. Laven JS,Mulders AG, Visser JA, Themmen AP,DeJong FH, Fauser BC. Antimullerian hormone Serum concentrations in normoovulatory and anovulatory women of reproductive age. J Clin Endocrinol Metab 2004;89:318-23.
59. Taieb J, Grynberg M,Pierre A, Arouche N, MasartP,Belville C ,etal.Peigne M, FSH and its second messenger cAMPstimulate the transcription of human Antimullerian hormone in cultured granulosa cells . Mol Endocrinol 2011; 25:645-55.
60. Barbotin AL, Peigne M, Malone SA, Giacobini P.Emerging roles of Antimullerian hormone in hypothalamic-pituitary function. Neuroendocrinology 2019; 109:218-29.
61. Garrel G,Denoyelle C,L'Hote D,Picard JY,Tixiera J,Kaiser UB,etal.GnRH transactivates human AMH receptor gene via Egr1 and FOXO1 in gonadotrope cells. Neuroendocrinology 2019; 109:65-83.
62. Hall JE, Taylor AE, Hayes FJ, Crowley FJ.Insights into hypothalamic-pituitary dysfunction in polycystic ovary syndrome. J Endocrinol Invest 1998; 21:602-11.
63. Bry-Gauillaird H,Larrat Ledoux F,Levaillant JM,Massin N,Maione I,Beau I,etal. Antimullerian hormone and ovarian morphology in women with hypogonadotropic hypogonadism/kallmann syndrome:effects of recombinant human FSH. . J Clin Endocrinol Metab 2017; 102:1102-11.
64. Marshall JC, Griffin ML.The role of changing pulse frequency in the regulation of ovulation. Human Reprod 1993;8(Suppl2):57-61.
65. Abbott DH, Dumesic MA, Frank S. Developmental origin of polycystic ovary syndrome.JEndocrinol 2002; 174:1-5.
66. Stener –Victorin E, Padmanabhan V, Walters KA, Campbell RE, Benrick R, Giacobini P, etal. Animal models to understand the etiology and pathophysiology of polycystic ovary syndrome.Endocr Rev 2020; 41:538-76.
67. Tata B,,Mimouni NH, Barbotin AL, Malone SA,Loyens A, Pigny P,etal.Elevated prenatal Antimullerian hormone reprograms the fetus and induces Polycystic ovary syndrome at term. Nat Med 2018;24:834-46.
68. Maliqueo M,Sun M,Johansson J,Benricke A,Labrie F,Svensson H,etal.Continuous administration of a P450 aromatase inhibitor induces Polycystic ovary syndrome with a metabolic and endocrine phenotype in female rats at adult age. Endocrinology 2013; 154:434-45.
69. Maliqueo M,Lara HE,Sanchez F,Echiburu B,Crisosto N,Sir Petermann T.Placental steroidogenesis in pregnant women with Polycystic ovary syndrome . Eur J Obstet Gynaecol Reprod Biol 2013; 166:151-5.
70. Sahmay S,Aydogan Mathyk B,Sofiyeva N,Atakul N,Azemi A,Erei T. Serum AMH level and insulin resistance in women with PCOS. Eur J Obstet Gynecol Reprod Biol2018 ;224:159-164. doi: 10.1016/j.ejogrb.2018.03.007.
71. Wiweko B,Indra I,Susanto C,Natadisatra M,Hestiant0ro A.The correlation between AMH and HOMA-IR among PCOS phenotypes.BMC Res Notes 2018;11(1):114. doi: 10.1186/s13104-018-3207-y.
72. Simpson S,Seifer DB,Shabanova V,Lynn AV,Howe C,Rowe E,etal.The association between Antimullerian hormone and Vitamin 25(OH) D serum levels and , Polycystic ovary syndrome in adolescent females. Reprod Biol Endocrinol2020 21; 18(1):118. doi: 10.1186/s12958-020-00676-y.

Figure 1



Courtesy ref no-41-Interaction between androgens, FSH, AMH, and E2 during folliculogenesis. From Dewailly et al. (19), with permission. Relationships between androgens, FSH and AMH during the gonadotropin-independent follicular growth phase (green triangle) and between FSH, AMH and estradiol during the gonadotropin- dependent follicular growth phase (red triangle). "+," "–," or "?" indicate a positive, negative or uncertain effect, respectively, from one of the factors on the other. During the gonadotropin-independent follicular growth phase, the inhibitory effect of AMH mainly influences the promoting effect of FSH on follicular growth (arrow 2). According to our theory, FSH, whose receptors are enhanced by androgens (arrow 1), would stimulate the AMH production during this phase (arrow 2 rev), in the absence of estradiol. A direct effect from androgens on AMH production (arrow 3) is unlikely (see text for details). During the gonadotropin-dependent follicular growth phase, AMH is also involved in a triangular relationship with FSH and estradiol. During this phase, the inhibitory effect of AMH influences mainly the cell differentiation functions induced by FSH (arrow 4), in particular the induction of aromatase (arrow 5). This inhibitory effect will gradually subside, which will allow induction of aromatase by FSH, with consequent synthesis of estradiol which will in turn accelerates the extinction of AMH secretion in large antral follicles (arrow 6).